

AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions of claims in the application.

Listing of Claims:

1. (Original) A chimeric binding protein that is immunogenic in a human, said chimeric binding protein being one that binds specifically to a first antibody idotype or a specific binding region of a ligand that binds a receptor present in an antigen of said human, wherein said chimeric binding protein comprises:

- a B-cell epitope in the form of a second antibody idotype, wherein said second antibody idotype specifically binds the first antibody idotype or specific binding region and which competes with the receptor for binding to the first antibody idotype or specific binding region,
- a scaffold protein structure that stabilises the 3D conformation of the second antibody idotype, said scaffold protein structure being derived from an immunoglobulin autologous in said human, and
- at least one tolerance breaking amino acid sequence, which is heterologous in said human and which binds to an MHC Class II molecule in said human.

2. (Original) The chimeric binding protein of claim 1, wherein said scaffold protein structure is derived from IgG.

3. (Currently Amended) The chimeric binding protein of claim 1 or 2, wherein said scaffold protein structure is derived from the non-idiotypic region of a molecule selected from the group consisting of a complete antibody, an F(ab')₂ fragment, an Fab fragment, and an scFv.

4. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-3~~, wherein said scaffold protein structure comprises a substantially complete amino acid sequence of an immunoglobulin autologous in said human.

5. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-4~~, wherein said scaffold protein structure comprises a substantial number of B-cell epitopes found in the autologous scaffold protein structure in the human.

6. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-5~~, wherein said scaffold protein structure has substantially the same tertiary structure of an immunoglobulin autologous in said human ~~animal~~.

7. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-6~~, wherein said first antibody idiotype is the idiotype of a monoclonal antibody.

8. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-7~~, wherein said tolerance breaking amino acid sequence is introduced by means of amino acid insertion or substitution in the amino acid sequence of the scaffold protein structure.

9. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-8~~, which is an anti-idiotypic antibody or an effectively binding fragment thereof that is modified so

as to include said tolerance breaking amino acid sequence.

10. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-9~~, wherein the antigen of said human animal that includes said ~~second~~ receptor is selected from the group consisting of immunoglobulin E, CD20, CD11a, beta amyloid, HER-2, and TNF α .

11. (Currently Amended) The chimeric binding protein of claim 1 ~~any one of claims 1-10~~, which further comprises

- at least one first moiety which effects targeting of the chimeric binding protein to an antigen presenting cell (APC) or a B-lymphocyte, ~~and/or~~
- at least one second moiety which stimulates the immune system, ~~and/or~~
- at least one third moiety which optimises presentation of the chimeric binding protein to the immune system.

12. (Currently Amended) The chimeric binding protein of ~~according to~~ claim 11, wherein the tolerance breaking amino acid sequence, ~~and/or~~ the first moiety, ~~and/or~~ the second moiety, ~~or and/or~~ the third moiety is ~~is/are~~ present in the chimeric binding protein by being bound to suitable side groups in the scaffold protein structure.

13. (Currently Amended) The chimeric binding protein of ~~according to~~ claim 12, wherein the tolerance breaking amino acid sequence, ~~and/or~~ the first moiety, ~~and/or~~ the second moiety, ~~or and/or~~ the third moiety is ~~is/are~~ present in the scaffold protein structure by means of at

least one amino acid substitution, ~~and/or~~ deletion, ~~and/or~~ insertion, or ~~and/or~~ addition.

14. (Currently Amended) The chimeric binding protein of claim 1 ~~according to any one of claims 1-13~~, wherein the tolerance breaking amino acid sequence is promiscuous in humans.

15. (Currently Amended) The chimeric binding protein of claim 1 ~~according to any one of claims 1-14~~, wherein the tolerance breading amino acid sequence is selected from a natural promiscuous T helper cell epitope and an artificial MHC-II binding peptide sequence.

16. (Currently Amended) The chimeric binding protein of ~~according to~~ claim 15, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagglutinin epitope, and a P. falciparum CS epitope, and wherein the articial MHC-II binding peptide sequence is a PADRE peptide.

17. (Currently Amended) The chimeric binding protein of claim 11 ~~according to any one of claims 11-16~~, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC specific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

18. (Currently Amended) The chimeric binding protein of claim 11 ~~according to any one of claims 11-17~~, wherein the second moiety is selected from a cytokine and a heat-shock protein.

19. (Currently Amended) The chimeric binding protein of ~~according to~~ claim 18, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN- γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and the heat-shock protein is selected from, or is an effective part of any of, HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT).

20. (Currently Amended) The chimeric binding protein of claim 11 ~~according to any one of claims 11-19~~, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

21. (Currently Amended) A nucleic acid fragment that encodes the chimeric binding protein of claim 1 ~~according to any one of claims 1-20~~, or a nucleic acid fragment complementary thereto.

22. (Currently Amended) A vector carrying the nucleic acid fragment of ~~according to~~ claim 21, such as a vector that is capable of autonomous replication.

23. (Currently Amended) The vector of ~~according to~~ claim 22, which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

24. (Currently Amended) The vector of ~~according to~~ claim 22 ~~or 23~~, comprising, in the

5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment of according to claim 21, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment of according to claim 21, and optionally a terminator.

25. (Currently Amended) The vector according to claim 22 ~~any one of claims 22-24~~ which, when introduced into a host cell, is capable or incapable of being integrated in the host cell genome.

26. (Currently Amended) The vector of claim 24 ~~according to any one of claims 22-25~~, wherein said a promoter drives expression in a eukaryotic cell or ~~and/or~~ in a prokaryotic cell.

27. (Currently Amended) A transformed cell carrying the vector of claim 22 ~~any one of claims 22-25~~, such as a transformed cell which is capable of replicating the nucleic acid fragment of according to claim 21.

28. (Currently Amended) The transformed cell of according to claim 27, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multi-cellular organism selected from a fungus, an insect cell such as an S2 or an SF cell, a plant cell, and a mammalian cell.

29. (Currently Amended) The transformed cell of claim 27 ~~according to claim 27-28~~,

which expresses the nucleic acid fragment of defined in claim 21, such as a transformed cell, which secretes or carries on its surface, the chimeric binding protein of claim 1 defined in any one of claims 1-20.

30. (Currently Amended) A composition for inducing production of antibodies against an antigen in the autologous host, the composition comprising

- a chimeric binding protein of claim 1 according to any one of claims 1-20, and
- a pharmaceutically and immunologically acceptable carrier, and/or vehicle, or and/or adjuvant.

31. (Currently Amended) A composition for inducing production of antibodies against an antigen in the autologous host, the composition comprising

- a nucleic acid fragment of according to claim 21 or a vector of claim 22 according to any one of claims 22-26, and
- a pharmaceutically and immunologically acceptable carrier, and/or vehicle, or and/or adjuvant.

32. (Currently Amended) A stable cell line which carries the vector of claim 22 according to any one of claims 22-26 and which expresses the nucleic acid fragment of according to claim 21, and which optionally secretes or carries the chimeric binding protein of claim 1 according to any one of claims 1-20 on its surface.

33. (Currently Amended) A method for the preparation of the cell of claim 27 according to any one of claims 27-29, the method comprising transforming a host cell with the nucleic acid

fragment ~~of according to~~ claim 21 or with the vector of claim 22 ~~according to any one of claims 22-26.~~

34. (Currently Amended) A method for preparing the chimeric binding protein of claim 1 ~~any one of claims 1-20~~, the method comprising the following steps:

- 1) providing a first molecule, which binds to a self-antigen of interest in a human and which includes the first antibody idiotype or said specific binding region,
- 2) immunizing, with the first molecule optionally being coupled to an immunogenic carrier, a transgenic animal that produces antibodies that are autologous in humans or that are autologous in humans except for the fact that they also include at least one amino acid sequence that breaks tolerance in humans,
- 3) preparing and isolating hybridomas that produce antibodies that bind the first molecule,
- 4) screening the hybridomas of step 3 for their ability to produce antibodies that selectively bind to said first antibody idiotype or said specific binding region, and
- 5) transforming a suitable host cell with at least genetic material that encodes antibodies or functional parts thereof where the genetic material is or can be isolated from the hybridomas of step 4 that produce selectively binding antibodies,
- 6) culturing the host cells transformed in step 5 under conditions that facilitate production of at least the antibodies or functional fragments thereof, and recovering the antibodies or functional fragments thereof from the host cell culture.

35. (Cancelled)

36. (Currently Amended) The method of ~~according to~~ claim 34 ~~or 35~~, wherein the first molecule is an antibody, preferably a monoclonal antibody.

37. (Currently Amended) The method of ~~according to~~ claim 36, wherein the first receptor is the idiotype of the antibody.

38. (Currently Amended) The method of claim 34 ~~according to any one of claims 34-37~~, wherein the screening in step 3 includes an exclusion step that allows identification of members of the library that bind the first molecule outside the first antibody idiotype or specific binding region so as to exclude such members from subsequent steps.

39. (Currently Amended) The method of ~~according to~~ claim 38, wherein said exclusion step involves

a) a test of the library members' ability to bind to the parts of the first molecule that are outside the first antibody idiotype or specific binding region, so as to allow exclusion of library members that exhibit such binding, or ~~and/or~~

b) a test of the library members' ability to compete with the receptor of ~~defined in~~ claim 1 for binding to the first antibody idiotype or specific binding region that allows exclusion of library members that do not exhibit such ability.

40-51 (Cancelled)

52. (New) A method for preparing the chimeric binding protein of claim 1, the method comprising the following steps:

- 1) providing a first molecule, which binds to a self-antigen of interest in a human and which includes the first antibody idiotype or specific binding region,
- 2) screening a library of second molecules for their ability to selectively bind to said first antibody idiotype or specific binding region of said first molecule,
- 3) isolating the members of the library that selectively binds in step 2, and
- 4) preparing, by means of synthesis or recombinant technology, the chimeric binding protein that contains at least a) a second antibody idiotype present in a member isolated in step 3, b) a scaffold protein structure derived from an immunoglobulin, which is autologous in the human and which stabilises the native 3D structure of said second antibody idiotype, and c) a non-human MHC Class II binding amino acid sequence.

53. (New) The method of claim 52, wherein the first molecule is an antibody, preferably a monoclonal antibody.

54. (New) The method of claim 53, wherein the first receptor is the idiotype of the antibody.

55. (New) The method claim 52, wherein the screening in step 3 includes an exclusion step that allows identification of members of the library that bind the first molecule outside the

first antibody idiotype or specific binding region so as to exclude such members from subsequent steps.

56. (New) The method of claim 55, wherein said exclusion step involves

- a) a test of the library members' ability to bind to the parts of the first molecule that are outside the first antibody idiotype or specific binding region, so as to allow exclusion of library members that exhibit such binding, or
- b) a test of the library members' ability to compete with the receptor of claim 1 for binding to the first antibody idiotype or specific binding region that allows exclusion of library members that do not exhibit such ability.

57. (New) The method of claim 52, wherein step 3 involves phage display of the second molecules.

58. (New) The method of claim 52, wherein step 3 involves that the library of second molecules is subjected to ribosome display, mRNA-display, or yeast surface display.

59. (New) A method for down-regulating an antigen or a cell that displays epitopes of said antigen in a human, the method comprising presenting the human's immune system with an immunogenically effective amount of the chimeric binding protein of claim 1 so as to induce a specific immune response against the self-antigen that includes in its structure the receptor of claim 1.

60. (New) The method of claim 59, wherein an effective amount of the chimeric binding protein is administered to the animal via a route selected from the parenteral route such as the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublingual route; the epidural route; the spinal route; the anal route; and the intracranial route.

61. (New) The method of claim 60, wherein the effective amount is between 0.5 μ g and 2,000 μ g of the chimeric binding protein.

62. (New) The method of claim 59, wherein the chimeric binding protein is contained in a virtual lymph node (VLN) device.

63. (New) The method of claim 59, wherein the chimeric binding protein has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

64. (New) The method of claim 59, wherein presentation of the chimeric binding protein to the immune system is effected by introducing nucleic acid(s) encoding the chimeric binding protein into the animal's cells and thereby obtaining in vivo expression by the cells of the nucleic acid(s) introduced.

65. (New) The method of claim 64, wherein the nucleic acid(s) introduced is/are selected

from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant.

66. (New) The method of claim 65, wherein the nucleic acid(s) is/are contained in a VLN device.

67. (New) The method of claim 59, which includes at least one administration/introduction per year.

68. (New) The method of claim 59, wherein said administration/introduction occurs at least twice per year.

69. (New) The method of claim 59, wherein said administration/introduction occurs at least three times per year.

70. (New) The method of claim 59, wherein said administration/introduction occurs at least four times per year.

71. (New) The method of claim 59, wherein said administration/introduction occurs at

least six times per year.

72. (New) The method of claim 59, wherein said administration/introduction occurs at least twelve times per year.

73. (New) The method of claim 59, wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying and expressing the nucleic acid fragment of claim 21.